REMARKS

Claim Status

Claims 6, 7, 13, 16-41, 47 and 48 are cancelled. Of these, claims 27-30, 32 and 35-41 were withdrawn by the Examiner as being directed to an invention (group III) different from the invention (group I) recited in the pending claims (refer to March 21, 2008 Restriction Requirement). Applicants reserve the right to file one or more divisional applications in the future to pursue the subject matter of the cancelled claims.

Claims 44-46 are withdrawn. These claims recite non-elected subject matter (refer to March 21, 2008 Restriction Requirement). Pursuant to the examination guidelines regarding restriction practice and generic claims (MPEP § 809), Applicants will seek to rejoin these claims if claim 1 is deemed allowable. The Examiner decided to examine claim 43 in formulating the pending Office Action, though Applicants had requested in the July 21, 2008 Response that this claim be withdrawn.

Claims 1, 3-5, 12, 43, 45 and 46 are currently amended. The amended claims are supported by the original specification. For example, the first "wherein" clause recited in claim 1 is supported by paragraphs 57 and 58. The second "wherein" clause of claim 1 is derived from original claim 2, for example.

Claim 49 is new and has written support throughout the specification (e.g., Table 4).

Applicants respectfully submit that the foregoing amendments to the claims do not introduce any new subject matter to the application. With the present amendments, there are eighteen claims pending, namely claims 1-5, 8-12, 14, 15 and 42-49.

Restriction Requirement

The restriction between invention groups I and III as imposed in the March 21, 2008 Restriction Requirement is maintained and finalized by the Examiner. However, the Examiner withdraws (i) the restriction requirement between wildtype *E. coli* glutamate dehydrogenase (GDH, SEQ ID NO:2) and the K92L version thereof (SEQ ID NO:4), and (ii) the restriction requirement as it related to electing a particular heterologous protein (e.g., somatotropin). Applicants appreciate the Examiner's consideration of the restriction requirement traversal provided in the May 21, 2008 Response.

The comments in the pending Office Action specify that the claims have been examined insofar as they relate to two sequences: "For examination purposes, the Examiner will only examine the elected invention, a method of using the glutamate dehydrogenase of SEQ ID NO:2 or 4" (page 3, lines 6-78; emphasis added). However, in lodging certain rejections (e.g., the first obviousness rejection, Office Action, page 15), the Examiner seems to have extended examination to the claims that are generic to those reciting SEQ ID NOs:2 and 4. Hence, though Applicants mostly tailor the following remarks with regard to *E. coli* GDH, certain remarks are also provided regarding the NSAADP genus as currently claimed.

Claim Rejections – 35 USC § 112, second paragraph

Claims 3 and 12 stand rejected under 35 USC § 112, second paragraph, as being indefinite. Regarding the recitations "K92L" and "lysine 92 leucine," the Examiner alleges that the "[a]mino acid position corresponding to a specific position can be easily confused depending on how sequences are aligned" (page 4, lines 9-11).

Claim 3 as amended recites the K92L form of *E. coli* GDH in a different, but equivalent, manner compared to the previous rendition of the claim. Applicants respectfully submit for the

following reasons that skilled artisans would not be confused by the recited terminology. Please find attached with this Response amino acid sequences for *E. coli* GDH as previously determined by various parties; these sequences are catalogued in the National Center for Biotechnology Information (NCBI) website under accession numbers NP_416275, AAA23868, NP_288194, NP_754056 and ZP_03049943 (arrows indicate dates prior to the instant filing date in which each particular sequence was disclosed via publication or direct submission to NCBI). All these sequences are 447 amino acids in length and are highly conserved. Sequences under NCBI accession numbers YP_002407302 and YP_001463059 are also provided; although these particular sequences were disclosed after the filing date, they further serve to demonstrate the high conservation of *E. coli* GDH.

Given this uniformity in length and sequence, skilled artisans would readily be able to determine whether a particular *E. coli* GDH sequence has a lysine or leucine residue at position 92. All that would be required would be to align the selected *E. coli* GDH sequence with one or more of the above reference sequences, which all have a lysine at position 92. In view of the above amendments and remarks, Applicants respectfully submit that this rejection is overcome.

Claim Rejections – 35 USC § 112, first paragraph (Written Description)

Claims 1-5, 8-12, 14-18, 42, 43, 47 and 48 stand rejected under 35 USC § 112, first paragraph, as lacking written description by the specification. The Examiner contends that the specification does not reasonably convey that "the inventor(s), at the time the application was filed, had possession of the claimed invention."

In lodging this rejection, the Examiner partly alleges that the specification does not support the terminology "a sequence selected from..." in claims 4 and 5, which recite specific sequences. This language allegedly reads on short fragments of the recited sequences. These

claims are currently amended to recite that the non-standard amino acid degrading protein (NSAADP) comprises a specific sequence.

The Examiner cites to *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398) in alleging that certain genera recited in the claims (e.g., NSAADP and GDH) do not have written support. In that case, the U.S. Court of Appeals for the Federal Circuit (CAFC) decided that the genus "vertebrate insulin cDNA" was not supported by the specification of the asserted patent. This decision took into account that (i) the specification disclosed only rat insulin cDNA, and (ii), at the time the asserted patent in *Eli Lilly* was filed, no other vertebrate insulin cDNAs were known in the field.

This set of circumstances regarding written description in *Eli Lilly*, however, does not apply to the instant application. As discussed in the above remarks (35 USC § 112, second paragraph), *E. coli* GDH enzymes were known in the art as of the instant application's filing date. The instant specification also makes certain disclosure of this enzyme in Table 4 (where "Source Species" is *E. coli*). Given this disclosure and the prior knowledge in the field, skilled artisans would acknowledge that Applicants did possess the claimed invention as it employs *E. coli* GDH.

The Examiner also alleges in leveling this rejection that the disclosure of *E. coli* GDH does not provide sufficient written support for the NSAADP genus as recited in the claimed method. It seems that this conclusion results in part from the examination being limited to the *E. coli* GDH sequences SEQ ID NOs:2 and 4. NSAADPs as recited in current claim 1 are directed to the following enzymes: glutamate dehydrogenase, leucine dehydrogenase, valine dehydrogenase, phenylalanine dehydrogenase and glutamate/leucine/phenylalanine/valine dehydrogenase. Applicants respectfully assert that the instant specification provides written

description for these particular NSAADPs. Table 4 (Tables 1 and 2 as well) discloses multiple examples of the NSAADPs recited in claim 1 – the structure and function of these enzymes were known to skilled artisans (note that sequences in Table 4 have been previously deposited with Genbank). Applicants respectfully contend just for the sake of argument that, in view of this prior knowledge, the inclusion of Table 4 in the specification would not technically be necessary to give written support to the currently recited NSAADPs ("The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public," MPEP § 2164.05[a]). Further, examples of the above NSAADPs are disclosed in the instant specification (Example 2, Table 5) to significantly reduce incorporation of norleucine in a heterologously expressed protein.

Applicants kindly wish to stress for the record that the invention as currently and previously claimed is directed to an innovative use of certain NSAADPs. These NSAADPs themselves do not constitute the invention – indeed, they are already well known in the art – but rather how they can be employed in reducing norleucine incorporation in heterologously expressed proteins.

In view of the above amendments and remarks, Applicants respectfully submit that the pending claims have written support by the specification.

Claim Rejections – 35 USC § 112, first paragraph (Enablement)

Claims 1-5, 8-12, 14-18, 42, 43, 47 and 48 stand rejected under 35 USC § 112, first paragraph, as not being enabled by the specification.

In lodging this rejection, the Examiner partly alleges that the specification does not enable the terminology "a sequence selected from..." in claims 4 and 5, which recite specific sequences. This language allegedly reads on short fragments of the recited sequences. These claims are

currently amended to recite that the non-standard amino acid degrading protein (NSAADP) comprises a specific sequence.

The Examiner partly alleges that the specification does not provide enablement for "a method of using any or all polypeptides having non-standard amino acid degrading activity, but having unknown structure." The current claims recite certain enzymes (glutamate dehydrogenase, leucine dehydrogenase, valine dehydrogenase, phenylalanine dehydrogenase, glutamate/leucine/phenylalanine/valine dehydrogenase) as the NSAADPs that can be employed in the method. As discussed in the above remarks, the structures of these enzymes are well known in the art and examples thereof are disclosed in the instant specification to significantly reduce incorporation of norleucine in a heterologously expressed protein (Example 2, Table 5). Given this information, skilled artisans would readily be able to practice the claimed invention.

In leveling comments regarding the breadth of the previous claims, the Examiner alleges in part that the claims

> ...encompass a method of using (A) any or all non-standard amino acid degrading protein[s] isolated from any source, including any or all mutants, recombinants and variants thereof, (B) any or all glutamate dehydrogenases, isolated from any or all source[s], including any or all mutants, recombinants and variants thereof...

Office Action, page 10, lines 12-15. The Examiner then alleges in further comments that these "mutants, recombinants and variants" are not enabled by the specification given reasons such as predictability and level of experimentation required. Brandon et al. (1991, Introduction to Protein Structure, page 247) is cited by the Examiner to document the alleged unpredictability of amino acid changes on protein function. The following remarks by Applicants are made insofar as these allegations might apply to enablement of the currently amended claims.

Recent decisions by the U.S. Patent Office Board of Patent Appeals and Interferences speak to the enablement of modified versions of known proteins and nucleic acids, despite the unpredictability and experimental issues surrounding modifications. In its decision, *Ex parte Kubin* (2007, attached; page 14, line 13 – page 15, line 6), the Board agreed with the appellants' argument that only routine experimentation would be required by skilled artisans to test the operability of modified proteins (the examiner in the appealed application had leveled arguments similar to the above allegations):

> We agree with the Examiner that molecular biology is generally an unpredictable art (and thus was so at the time the application was filed). However, with respect to enablement, the other *Wands* factors weigh in Appellants' favor, particularly "the state of the art" and "the relative skill of those in the art,"...The amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine.

Ex parte Kubin, page 14, lines 16-25. The Board made a similar ruling in its decision, *Ex parte Heck* (2008, attached; page 8, line 12 – page 12, line 14) – this time regarding modifications to nucleic acids – when presented with issues similar to those considered in *Ex parte Kubin*:

> Even if we were to assume that the amount of experimentation might be extensive, such experimentation would have been routine...The methods for performing such screening were provided by the Specification, and were also well known to those skilled in the art. *See, e.g., Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) ("test [for undue experimentation] is not merely quantitative...if it is merely routine"); *Ex parte Kubin*, 83 USPQ2d 1410, 1416 (Bd. Pat. App. & Int. 2007). Thus, we conclude the Specification provides an enabling disclosure.

Ex parte Heck, page 12, lines 3-14.

The structure and function of the NSAADPs recited in the instant application are well known in the art (refer to above remarks regarding 35 USC § 112, first paragraph). Although certain modifications (e.g., amino acid changes) to these NSAADPs may impair their activity such that they would be inoperable in the claimed method, it would have been well within the

skill in the art to screen for those modified NSAADPs that do properly function. The structural/functional information gathered for certain GDH mutants as disclosed in the references cited in the pending obviousness rejections (Wang et al., Rice et al.; discussed below) serves as but one example of this skill level.

In view of the above amendments and remarks, Applicants respectfully submit that the pending claims are enabled by the specification.

Claim Rejections – 35 USC § 103(a)

Two different obviousness rejections under 35 USC § 103(a) are lodged in the pending Office Action. In the first rejection, claims 1, 2, 8-11, 14-18, 42, 43, 47 and 48 are alleged to be obvious over the combination of Wang et al. (2001, *Eur. J. Biochem.* 268:5791-5799), Bogosian et al. (U.S. Patent No. 5,932,439) and Fenton et al. (U.S. Patent No. 5,599,690). In the second rejection, claims 3-5 and 12 are alleged to be obvious over the combination of Wang et al., Bogosian et al., Fenton et al. and Rice et al. (1996, *FEMS Microbiol. Rev.* 18:105-117).

The Examiner alleges in part that Wang discloses a mutant GDH that has increased activity for degrading norleucine; this GDH carries a K89L amino acid change and is derived from *Clostridium symbiosum*. As disclosed by Rice, *C. symbiosum* K89L GDH is allegedly of similar structure to *E. coli* K92L GDH, where position 89 in the former enzyme corresponds to position 92 in the latter enzyme (Rice also alleges that the wildtype forms of these enzymes are structurally similar). Fenton is cited to establish that the field already knew that non-standard amino acid incorporation in heterologously expressed proteins is problematic, thus allegedly providing a motive for skilled artisans to use the GDH's taught by Wang and Rice in deriving the currently claimed invention. Bogosian is cited simply to establish that heterologous protein (e.g., somatotropin) expression was a previously known practice.

The K89L GDH taught by Wang is known to degrade the standard amino acid methionine; this is disclosed, for example, in Stillman et al. (1999, *J. Mol. Biol.* 285:875-885, page 876, 2nd column, lines 39-44), which is of record in the instant application (March 20, 2006 Information Disclosure Statement). The double- and triple-mutant forms of K89L GDH taught by Wang also have methionine-degrading activity (page 5794, 2nd column, lines 1-7). Given this activity, skilled artisans would not have been motivated to overexpress forms of *C. symbiosum* GDH comprising K89L or its equivalent counterparts such as *E. coli* K92L GDH: such mutants would have been expected to impede expression of heterologous proteins. Methionine is required for protein translation in bacteria, since it is used as the first residue in all proteins, as well as at internal positions in most proteins. In the same vein, skilled artisans would not have been motivated to overexpress wildtype *C. symbiosum* GDH or its equivalents (*E. coli* GDH) in a bacterial protein expression system. Wildtype GDH degrades the standard amino acid glutamate, which is common to most proteins; this enzyme too would be expected to negatively impact heterologous protein production when overexpressed.

The motivation to use wildtype and mutant forms of GDH in the currently claimed method is further eroded by the unpredictability inherent to extending *in vitro* enzymatic observations (i.e., those of Wang) to *in vivo* conditions. The results discussed below regarding the surprising effectiveness of wildtype *E. coli* GDH in the claimed method exemplify this unpredictability.

The claimed invention also provided unexpected results. When applying the currently claimed method as described in Example 2 of the specification, Applicants were able to produce recombinant somatotropin for amino acid content analysis. Such expression of a heterologous

protein is surprising in view of the negative effects on protein translation that would have been expected to occur in attempting to overexpress NSAADPs (refer to above remarks).

The results disclosed in Example 2 of the specification are also surprising for another reason. As discussed in the pending Office Action, Wang discloses that K89L *C. symbiosum* GDH has norleucine-degrading activity. However, this activity is taught by Wang to be absent with wildtype GDH (e.g., Tables 1 and 4, norleucine is abbreviated as "Nle"). Despite this lack of norleucine-degrading activity, Applicants observed a reduction of norleucine incorporation in heterologously expressed somatotropin – from 17.4% to 0.9% – when practicing the claimed invention with the wildtype counterpart of *C. symbiosum* GDH from *E. coli* (specification, Table 5). This reduction is almost equal to that obtained when overexpressing *E. coli* K92L GDH. The ability of wildtype GDH to effect such an effective reduction in norleucine levels would not have been expected by skilled artisans in consideration of Wang.

Given the above remarks concerning lack of motivation, unpredictability and unexpected results, Applicants respectfully submit that both of the pending obviousness rejections should be withdrawn.

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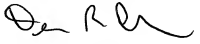
Aside from the fee for a one-month extension of time, no other fee is believed to be due in connection with this response. However, the Commissioner is hereby authorized to charge any underpayment of fees to Howrey LLP Deposit Account No. 08-3038/11916.0059.PCUS01.

Respectfully submitted,



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